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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Michael L Goldman
Nixon Peabody LLP
Clinton Square
P O Box 31051
Rochester, NY 14603

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,129	MAINES, MAHIN D.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 68-77 are pending.

Applicant's cancellation of claims 1-67, amendment of claims 68, 72, 73, 74 and addition of claim 77, in Paper No. 13, filed on 5/21/2003 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 68-70 and 73-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 68-70 and 73-77 are directed in part to a method of regulating protein kinase C by contacting protein kinase C with a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17. While Applicants submit that deleting the term "variants" and substituting it with the term "a polypeptide comprising the amino sequence of SEQ ID NO: 16 or 17" is supported by the specification, in particular Examples 1 and 3, the Examiner is unable to locate adequate

support in the specification for the use of polypeptides comprising the amino acid sequences of SEQ ID NO: 16 or 17. It is noted that according to the specification (page 10, lines 22-24), the peptides of SEQ ID NO: 16 and 17 have been defined as a protein kinase C enhancing domain and a protein kinase C inhibiting domain, respectively. There is also no disclosure in the specification of these peptides as variants of a mammalian biliverdin reductase with protein kinase C regulatory activity. Thus, there is no indication that a method for regulating any protein kinase C which uses a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17 was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

3. Claims 68-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. This rejection, which has been discussed in Paper No. 12, mailed on 11/19/2002, has been previously applied to claims 68-70 and 74-76 and is now applied to newly added claim 77 and claims 71-73 for the reasons of record and for the reasons set forth below.

5. Applicants argue that the instant application discloses 3 species of mammalian biliverdin reductase (BVR) as set forth in SEQ ID NO: 1, 3, and 4, functional domains of BVR, preparation of fragments of BVR, preparation of variants of BVR, and identification of BVR

fragments which have protein kinase C activity. Applicants submit an alignment of human, mouse and rat BVR to indicate the high sequence similarity among these BVRs. It is Applicant's opinion that based on the high sequence similarity between the mouse BVR and the human and rat BVRs, one of skill in the art would expect the mouse BVR to have protein kinase C regulatory activity. In view of the information provided by the specification and the alignment submitted, Applicants request withdrawal of the rejection.

6. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. Claims 68, 74-76 are directed to a method of regulating a genus of protein kinase C proteins using a genus of mammalian biliverdin reductases (BVR), fragments thereof having protein kinase C regulatory activity, or by a genus of polypeptides comprising the amino acid sequences of SEQ ID NO: 16 or 17. Claims 69 is directed to the method of claim 68 as described above with the added limitation that the PKC proteins regulated are those of the subgenus human. Claim 70 is directed to a method of regulating human protein kinase C isozymes α, β, γ with a genus of mammalian biliverdin reductases (BVR), fragments thereof having protein kinase C regulatory activity, or by a genus of polypeptides comprising the amino acid sequences of SEQ ID NO: 16 or 17. Claims 71-73 and 77 are directed to a method of regulating a genus of protein kinase C with a rat/human BVR, the polypeptides of SEQ ID NO: 1 or 3, or polypeptides comprising the peptides of SEQ ID NO: 16-18, 34 or 35. While the Examiner acknowledges the teachings of the specification in regard to the human and rat BVRs disclosed and the close structural homology between the mouse BVR and the human/rat BVRs, the Examiner disagrees with Applicant's contention that 2 human BVRs and one rat BVR are sufficient to adequately describe a large genus of BVRs. The genus "mammalian" encompasses

many more species than just human, rat and mouse. As indicated in previous Office Action Paper No. 12, the state of the art teaches the unpredictability of assigning function based on structural homology and clearly indicates that small structural changes can lead to major changes in function. See the teachings of Bork, Van de Loo et al., Seffernick et al. and Broun et al. already discussed. Therefore, it is unclear as to how one of skill in the art can reasonably conclude that a large genus of proteins can be adequately described with 3 structures disclosed by Applicants (human and rat) and 1 disclosed by the prior art (mouse). While Applicants have disclosed several functional domains in regard to the human BVR of SEQ ID NO: 1 and have indicated that some of these domains are present in the additional human BVR disclosed (SEQ ID NO: 3), there is no disclosure as to which of these domains are essential to display the kinase regulatory activity desired. Furthermore, while the specification discloses that the peptide of SEQ ID NO: 34 stimulates PKC activity (Figure 12a; page 71, lines 26-31) and the peptide of SEQ ID NO: 19 inhibits PKC activity (Figure 12a; page 71, lines 25-32), no disclosure of the PKC regulatory activity of the other functional domains has been provided nor there is any disclosure as to which domains are associated with stimulation or inhibition of PKC with the exception of the peptides of SEQ ID NO: 34 and 19. No disclosure of the PKC regulatory activity of the peptides of SEQ ID NO: 16 or 17 could be found in the specification either.

As known in the art and disclosed by Applicants (page 74, lines 21-24), protein kinase C is a family of proteins comprising several isozymes with different specificity. In addition to isozymes α, β, and γ, there are other isozymes such as δ, ε, η/L and θ. The specification discloses the interaction between rat BVR and human PKC isozyme α, β and γ (page 70, lines 25-32; Figure 10) but disclosure of such interaction with other PKC isozymes has not been

shown. Furthermore, there is no disclosure of which are the structural elements in any PKC (from any source) which interact with BVR and are required for regulation by BVR, nor there is disclosure of whether such interaction occurs in the conserved regions common to any PKC isozyme. In view of the teachings of the art in regard to the different PKC isozymes, their specificities and functions as well as the lack of information as to whether PKC isozymes from other sources in addition to human PKC isozymes α, β and γ can be regulated by BVR, it is unclear as to how one of skill in the art can reasonably conclude that any protein kinase C isozyme from any source can be regulated by any mammalian BVR, or even the BVRs of SEQ ID NO: 1, 3 or the peptides of SEQ ID NO: 18-19, or 34-35. Therefore, for the reasons set forth above, one of skill in the art cannot reasonably conclude that the claimed invention is adequately described.

7. Claims 68-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating the activity of human protein kinase C isozymes α, β and γ with the biliverdin reductase of SEQ ID NO: 1, 3 or the peptides of SEQ ID NO: 18, 19, 34 and 35, does not reasonably provide enablement for a method for regulating the activity of human protein kinase C isozymes α, β and γ with any protein of any function comprising the peptides of SEQ ID NO: 18, 19, 34, 35, or a method for regulating the activity of any protein kinase C with (1) any mammalian biliverdin reductase, (2) any fragment of (1) with PKC activity, (3) the BVR of SEQ ID NO: 1, 3, or the peptides of SEQ ID NO: 18-19, 34-35, or (4) any protein comprising the peptides of SEQ ID NO: 18-19, 34-35. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

8. This rejection, which has been discussed in Paper No. 12, mailed on 11/19/2002, has been previously applied to claims 68-70 and 74-76 and is now applied to newly added claim 77 and claims 71-73 for the reasons of record and for the reasons set forth below.

9. Applicants argue that claim 68 has been amended to recite "mammalian" BVR and for the reasons discussed above, one of skill in the art can identify other mammalian BVRs. According to Applicants, Example 1 teaches how to determine if a mammalian BVR has BVR activity and Example 3 teaches how to determine if a mammalian BVR possess protein kinase C regulatory activity. Applicants also submit that Example 3 teaches how to identify fragments of mammalian BVRs with protein kinase C regulatory activity and that it discloses 2 fragments from rat BVR, 2 fragments from human BVR that possess protein kinase C regulatory activity, and consensus sequences as set forth in SEQ ID NO: 16 and 17.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While the Examiner acknowledges the teachings of the specification in regard to Examples 1 and 3, the Examiner disagrees with Applicant's contention that the full scope of the claims is enabled. As discussed above, the state of the art teaches the unpredictability of isolating functional homologs using sequence comparison as evidenced by the teachings of Bork, Van de Loo et al., Seffernick et al. and Broun et al. already discussed. No disclosure of the critical structural elements required in a mammalian polypeptide to display BVR reductase activity has been provided. Furthermore, there is no disclosure as to which of functional domains found in the human BVRs are essential to display the kinase regulatory

activity desired in any mammalian BVR, nor there is disclosure of which of these domains are associated with stimulation or inhibition of PKC activity with the exception of the peptides of SEQ ID NO: 34 and 19. See discussion above. Therefore, while testing for BVR activity or protein kinase activity is taught by the specification, testing an extremely large number of polypeptides to identify those which can stimulate or inhibit any protein kinase C isozyme would constitute undue experimentation. In addition, the specification fails to disclose practicing the claimed method with any protein kinase C isozyme from any source, nor there is any evidence that one can regulate any protein kinase C isozyme with any mammalian BVR, the BVR of SEQ ID NO: 1, 3, the peptides of SEQ ID NO: 18-19, 34-35, or any protein comprising the peptides of SEQ ID NO: 18-19, 34-35. See discussion above. Moreover, there is no teaching or suggestion that a protein of any size and function comprising the peptides of SEQ ID NO: 18-19, 34-35 will regulate human protein kinase C isozymes α, β and γ. In the absence of some knowledge or guidance as to which are the additional structural elements required in any protein of any size and function comprising the peptides of SEQ ID NO: 18-19, 34 or 35 to regulate human PKC isozymes α, β and γ, which PKC isozymes can be regulated by BVRs or which are the structural elements in any PKC isozyme required for any mammalian BVR, the polypeptides of SEQ ID NO: 1 or 3, the peptides of SEQ ID NO: 18-19, 34-35, or any protein comprising the peptides of SEQ ID NO: 18-19, 34-35, to be able to regulate PKC, one of skill in the art would have to go through the burden of undue experimentation to determine whether any protein of any size and function comprising the peptides of SEQ ID NO: 18-19, 34 or 35 can regulate human protein kinase C isozymes α, β and γ, which PKC isozymes can be regulated with any mammalian BVR, or which PKC isozymes can be regulated with the BVRs of SEQ ID NO: 1, 3,

or the peptides of SEQ ID NO: 18-19, 34-35. In view of the information disclosed, the lack of knowledge as to the critical structural elements required to display BVR activity or PKC regulatory activity as discussed above, and the state of the art in regard to the unpredictability of isolating functional homologs using structural homology, one cannot reasonably conclude that the specification provides sufficient guidance to practice the claimed method.

11. Claims 68-75 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating the activity of human protein kinase C isozymes α, β and γ with the human biliverdin reductase of SEQ ID NO: 1 or 3 or the peptides of SEQ ID NO: 18, 19, 35 or 35 *in vitro*, does not reasonably provide enablement for such method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

12. It is noted that due to a typographical error, claim 68 was accidentally omitted from the list of rejected claims. Applicants correctly determined this typographical error and have responded to the rejection accordingly, as stated in the response, page 7, lines 1-3. The Examiner apologizes for any inconvenience this may have caused.

13. This rejection has been previously discussed in Paper No. 12, mailed on 11/19/2002 and is now applied to newly added claim 77 for the reasons of record.

14. Applicants argue that the specification discloses a number of techniques for introducing BVR into a patient and that BVR administration can be performed for purposes of regulating PKC activity in any one of a number of conditions in which PKC has a demonstrated role in

disease pathology, therefore according to Applicants, the specification teaches a description of in vivo uses of BVR, fragments thereof with PKC regulatory activity and polypeptides comprising the amino acid sequences of SEQ ID NO: 16 or 17. In addition, Applicants indicate that much is known about the biological role of PKC and that PKC inhibitors have been shown to prevent damage in focal and central ischemic brain injury and brain edema (Hara et al., J. Cereb. Blood Flow Metab. 10:646-653, 1990; cited in previous response Paper No. 11) as well as in preventing tumor growth in animals. Applicants submit that Meyer et al. (Int. J. Cancer 43:851-856, 1989; cited in previous response Paper No. 11) demonstrate the correlation between in vitro inhibition of PKC and in vivo inhibition of PKC using a PKC inhibitor. Therefore, Applicants conclude that in view of Meyer et al., one of skill in the art would expect other in vitro regulators of PKC to behave similarly in vivo.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While the Examiner acknowledges the teachings of Meyer et al., Hara et al., the teachings of the art in regard to other PKC inhibitors, and the teachings of the specification in regard to techniques for BVR delivery to a patient, the Examiner disagrees with Applicant's contention that the specification discloses how to practice the claimed method in vitro and that one of skill in the art would expect in vitro regulators of PKC activity to behave similarly in vivo. The specification (page 24, line 30-page 25, line 2) states a list of conditions in which the PCK role in disease pathology has been demonstrated and suggests that fragments or variants of BVR which are inhibitors can be useful in treatment of these diseases. However, no disclosure has been made of the use of any mammalian BVR, the BVR of SEQ ID NO: 1, 3, or the peptides of SEQ ID NO: 18-19 or 34-35 in a method to regulate any PKC *in vivo*.

Moreover, there is no disclosure of which of these polypeptides can be used as inhibitors of PKC activity with the exception of the peptide of SEQ ID NO: 19. See discussion above. Furthermore, as already discussed, the specification is silent in regard to the structural elements required in these polypeptides to be inhibitors or stimulators of PKC activity.

As indicated in previous Office Action Paper No. 12, those of skill in the art recognize that in vitro assays cannot be used to extrapolate *in vivo* results due to the increased complexity and cell-cell interaction of the *in vivo* environment. In the instant case, PKCs are involved in cell-surface signal transduction and their activity is highly regulated by the many interactions among different cells and interactions between the cells and the environment. Therefore, it is unclear as to how one of skill in the art can reasonably expect in vitro results to be extrapolated *in vivo*. In regard to the teachings of Meyer and Hara, it is noted that at best, one can conclude that a staurosporine derivative which has been shown to inhibit PKC *in vitro* may inhibit PKC *in vivo*. Therefore, neither these references, the specification or the state of the art teach or suggest the use of BVR to regulate PKC *in vivo*.

Conclusion

16. No claim is in condition for allowance.

17. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the

original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
July 25, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600